2017404

THE AMERICAN COUNCIL
ON SCIENCE AND HEALTH PRESENTS

SPECIAL REPORT

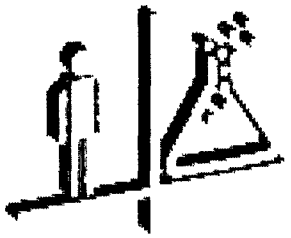
Perchlorate in Drinking Water
Scientific Collaboration in Defining Safety

Prepared for the
American Council on Science and Health (ACSH)
New York, NY

by Daland R. Juberg, Ph.D.
International Center for Toxicology and Medicine
Rochester, NY

Project Coordinator
Jeff Stier, Esq.
Associate Director, ACSH

January 2002



DR. ELIZABETH M. WHELAN
PRESIDENT

ACSH
1995 BROADWAY
2ND FLOOR
NEW YORK, NY
10023-5860

January 2002

Executive Summary

Since the mid-1990s, there has been an increasing amount of research effort aimed at evaluating the potential human health risk of perchlorate (ClO_4) because of its presence at trace levels in some water systems. Concern over potential effects on the thyroid gland in humans from perchlorate exposure and whether environmental levels pose a risk to human health have surfaced recently. In response to this concern, a broad collaborative effort spanning both private and government sectors has been engaged in extensive toxicological testing of perchlorate to add to our knowledge about how and under what exposure conditions perchlorate may cause effects in laboratory animals and in humans. The collaboration between the U.S. Environmental Protection Agency (EPA), the Department of Defense (Air Force) and an inter-industry Perchlorate Study Group (PSG) is unique in its focus on development of state-of-the art science for accurately determining what constitutes a safe level for humans.

Because of its mission to identify significant public health threats and to bring sound scientific analysis to environmental health concerns, the American Council on Science and Health (ACSH) has (a) evaluated the allegations of health risk from perchlorate as alleged by the Environmental Working Group (EWG); (b) reviewed the current regulatory process that is ongoing with respect to the establishment of a safe environmental exposure level; and (c) highlighted some of the recent scientific studies that have further characterized the toxicity of perchlorate in both animals and humans.

With respect to the EWG's Report entitled "Rocket Science" which alleges human health risk from perchlorate in drinking water, ACSH concludes the following:

- The EWG report encompasses a selective and limited use of the scientific data for perchlorate and does not represent the totality of our current knowledge regarding its toxicity.

- Many of the claims of health risk are not supported through the inclusion of scientific references and as such cannot be construed to represent the scientific facts.

- The EWG report mischaracterizes the current regulatory efforts

underway aimed at defining a safe exposure level and fails to recognize the scientific process at work.

- The EWG report has prematurely forecast what it believes to be a safe environmental exposure level without consideration of the significant amount of toxicological data that have been generated in the last few years or without regard for the scientific process at work.

In reviewing the history of the regulatory response in establishing a safe level for perchlorate in the environment, the ACSH concludes the following:

- Over the course of the last 10 years, the EPA has worked to define a safe exposure level for perchlorate in the environment, although a final value has not been established owing to data gaps for perchlorate.

- There has been a concerted effort to identify those studies and data gaps that would facilitate the establishment of a safe exposure level and significant testing has resulted in a much improved toxicological database for perchlorate.

- There has been a cooperative strategy and effort amongst both government and industry groups aimed at improving the scientific database for perchlorate for the protection of public health.

- As a result of the extensive toxicological testing, the EPA is expected to release its proposed Reference Dose (RfD, the safe exposure level for humans) in 2002, at which time all interested parties and stakeholders can publicly comment on the level.

In reviewing the recent scientific studies that have enhanced our knowledge of perchlorate's toxicity, ACSH concludes that:

- Both animal and human studies have appreciably contributed to our understanding of dose-response relationships for perchlorate such that the process of defining a protective RfD will be accompanied by less uncertainty and increased confidence.

- Both animal and human studies have contributed to our knowledge about the mechanism of action by which perchlorate exerts toxicity and under what exposure conditions. This knowledge will aid in the identification of sensitive subpopulations and in our increased ability to set a safe level for all humans.

- Because the number and types of toxicological studies that have been conducted for perchlorate has increased significantly, there is less uncertainty that accompanies the establishment of a safe exposure level and as such, the need for conservatism in the absence of knowledge has been reduced.

It is the intent of this ACSH report to provide readers with a perspective on how the concern over perchlorate arose, what the regulatory response has been over the last 10 years, and how the scientific process can be extremely beneficial in establishing safe exposure levels for humans in order to safeguard public health.

INTRODUCTION

What is Perchlorate?

Perchlorate is an anion that is both naturally occurring (e.g., such as in nitrate-mining regions of Chile) and man-made. It may be present in ground and surface waters as a result of the breakdown of ammonium, potassium, magnesium, or sodium salts that contain perchlorate (Crump et al., 2000; EPA, 1998). Ammonium perchlorate is manufactured primarily for use as an oxidizing agent in some military applications, principally as an ingredient in solid propellants for rockets and missiles. Because of its reducing capacity, it can undergo chemical reactions, which result in the release of gaseous products and it can thus act as a thrust booster. To this day, perchlorate remains an important component of the rocket delivery systems used in NASA and other space programs (EPA, 1998). In addition to its military applications, perchlorate has been used in airbags, stick matches and fireworks.

The Use of Perchlorate in Medicine

Normal thyroid function, which is dependent on an adequate supply of iodine, is important for growth and development. Normal thyroid function is especially important in fetal development, as hypothyroidism (deficiency of thyroid activity) during gestation often results in mental retardation (cretinism) in the neonate. If sufficient inhibition of iodine occurs, thyroid hormone production is depressed, which causes hypothyroidism. Perchlorate acts by inhibiting iodide uptake in the thyroid, and as a result of this, it was used to treat hyperthyroidism (excessive thyroid activity) due to Graves disease in the 1950s and 60s (Wolff, 1998; Stanbury and Wyngaarden, 1952; Trotter, 1962). Perchlorate has also been used to treat thyroid gland disorders resulting from overaccumulation of iodine, a side effect observed in some medical treatments (Bartalena et al., 1996). It is precisely because of its known action on the thyroid gland that the concern over human exposure to perchlorate from environmental sources arose. Clinical use of perchlorate in treating disease involves doses up to 400 milligrams on a daily basis, a level which is thousands of times greater than potential environmental exposures (Wolff, 1998).

The Current Concern

Because perchlorate has been detected at low levels in some water supply systems, primarily in the Western U.S., there has been some concern about whether its presence in the environment poses a health risk to humans. The U.S. EPA, in an effort to evaluate the potential risk and to establish a safe oral exposure level, has been actively engaged in testing and research on the toxicity of perchlorate over the past few years. Much of the current focus and debate centers on what exactly is an acceptable exposure level and on what scientific basis the EPA will establish its final Reference Dose (RfD) for humans. When the EPA releases its proposed RfD in early 2002, there will be an extensive peer review of the value to determine whether or not the RfD appropriately reflects the scientific database and knowledge that has developed for perchlorate.

in the 35-100 mg/day range, concentrations that are hundreds of times greater than any known human daily environmental exposure. Volunteer studies designed to determine the exposure level at which perchlorate begins to affect iodide uptake in humans show this level to be approximately 1 mg/day or 1000 µg/day, again, significantly higher than anticipated daily exposure (e.g., 30 µg/day) from drinking water (Soldin et al., 2001). The key point is that, collectively, the human epidemiological data support the lack of any effect on thyroid hormones or neurodevelopment at existing drinking water levels of perchlorate.

Chapter IV. The Commitment to Sound Science: Should the Public Be Concerned?

Where the Process Stands Today

Since mid-1999, the EPA (Office of Research and Development, or ORD) has been operating under an interim assessment guidance for perchlorate as outlined in a memo to all regional administrators (EPA, 1999). Essentially, the ORD guidance advises that EPA risk assessors and risk managers continue to use the standing provisional RfD range of 0.0001 to 0.0005 mg/kg/day for perchlorate-related assessment activities.

In terms of moving closer to the establishment of a final RfD, the EPA continues to collect information from those investigators that have conducted much of the research described in this report, both animal laboratory studies and human clinical studies. There are additional mechanistic and pharmacokinetic data that have been developed that are expected to be considered in the derivation of the RfD. The current schedule calls for the EPA to release its proposed RfD on January 15, 2002, with external peer review to follow in early March 2002. At the state level, the California Office of Environmental Health Hazard Assessment (OEHHA) is currently in the process of establishing a public health goal (PHG) for perchlorate in drinking water.

Identifying an Appropriate Study and Effect for RfD Development

EPA's draft RfD for perchlorate is based on a rat neurodevelopment study, using thyroid follicular-cell morphology changes at the lowest dose tested (0.1 mg/kg/day) as the critical effect. These changes were observed in rat pups (neonates) five days of age. Given the advances in our knowledge of perchlorate toxicity over the past several years, it is uncertain whether the EPA will retain this particular study and endpoint as the basis for its RfD or select another study and effect. That leads one to speculate as to what will be the critical effect (e.g., that effect upon which the RfD is based), what species or animal model will be selected, and what will be the underlying uncertainty factor associated with the RfD.

In developing the RfD, the EPA is likely to concentrate on the following:

- Hazard identification and data array analysis—In this step the EPA will organize the data by study type and purpose to determine available studies for RfD derivation.

- Designation of effect levels—In this step, the EPA will determine those critical levels at which effects were seen and, if possible, identify levels at which no effects were observed.

- Selection of a critical effect—This is an important step in that the EPA will need to identify what they perceive to be the most sensitive effect on the thyroid and the one that, if protected against, will protect against all other potential adverse effects.

- Dosimetric adjustment—If the critical study is an animal study, there will be some adjustment or extrapolation from animals to humans in terms of what a similar dose is for humans.

- Application of Uncertainty Factors—In the final step, the EPA will determine which uncertainty factors need to be applied (e.g., animal to human extrapolation, acute to chronic adjustment) and the size of each factor (range=1-10).

- Characterization of uncertainty—The EPA will describe in qualitative terms whether it has low, medium, or high confidence in the

overall RfD derived.

It is not the intent of this report to speculate on the critical study or endpoint of concern nor is it the purpose to go through a risk assessment process for perchlorate. However, as a result of our increased knowledge about perchlorate toxicity, there are several studies and findings that may be helpful in defining the RfD.

Given what we know about thyroid homeostasis and function and perchlorate's inhibition of iodine uptake, it appears that the developing fetus or pregnant mothers are the most sensitive individuals in terms of perchlorate's potential effects. The Argus-conducted neuropathology study (TERA, 2001), seeks to further refine this sensitivity by characterizing perchlorate-induced thyroid effects and alteration of hormone levels. The study is designed to evaluate thyroid histopathology and brain morphometry from both mothers and pups at multiple time points during gestation and lactation.

On the human level, the study by Greer et al. (2001) was conducted to identify the dose of perchlorate that would not cause inhibition of iodide uptake by the thyroid gland. Iodine uptake inhibition is a known precursor to other perchlorate effects and in this case, we have a human study (no need for extrapolation from animals) that has identified a no-effect level (again, a powerful finding for risk assessment) for this upstream or precursor event that is not itself considered adverse. The combination of these factors can be helpful in the risk assessment and definition of an RfD for perchlorate. First, the Greer et al. (2001) study was conducted in humans using both males and females. Second, the endpoint is one that advances the practice of risk assessment in that we are not just using the most sensitive adverse effect observed, but using a precursor event – a step that takes advantage of the science that has been developed. Third, there is inherent conservatism built into selection of this effect as it is not considered adverse per se, but rather precedes any thyroid toxicity. Because the relationship between iodine uptake inhibition and thyroid hormone changes is not precisely known, in this case, the use of a precursor event is prudent and conservative. Fourth, the study identified a no-effect level, which reduces uncertainty about effects in humans at the low end of the dose response curve. While pregnant females and developing fetuses were not a part of the study, some of the PBPK models and data that have been collected could be used to estimate a critical effect level for these sensitive humans.

Why Increases in the RfD Should Not be Alarming

Much of the EWG concern over regulatory policy for perchlorate is predicated on the fact that the provisional RfD for perchlorate has increased in recent years and that it may increase even further when the final EPA RfD is determined. EWG promulgates the perception that, by increasing the permissible exposure level, the safety standards for perchlorate are being eased or relaxed. Any increase in the RfD for perchlorate is the result of our ability to use new scientific information to reduce the uncertainty in former risk estimates for perchlorate. This process is encouraged and supported by the regulatory agencies, as it aids their ability to establish data-based exposure limits.

If the final RfD value is higher than in previous iterations of the provisional RfD, which it may well be, American consumers should not assume that this is a "less safe" value. Rather, this RfD results from intensive research on the toxicity of perchlorate. The end result has been to increase our knowledge of perchlorate, knowledge that has replaced uncertainty. On a practical level, many areas of uncertainty have now been delineated that heretofore were addressed by increasing the degree of uncertainty. Currently the EPA has a collective uncertainty factor of 100 for perchlorate; because of technological progress, the total uncertainty factor should soon be reduced to some lower value. While policy can always influence the determination of what constitutes a safe level, we now have sufficient science on perchlorate for the EPA to reduce, to an extent, its reliance on uncertainty factors as a primary means of protecting humans.

Using a Weight of Scientific Evidence Approach

The public should take comfort in knowing that the EPA's RfD for perchlorate, although based on one study and one endpoint of concern, is backed up by a considerable wealth of scientific information and data which increase our confidence in the safety of what the EPA defines as the RfD. Much of that information comes from additional animal studies that have evaluated different aspects of perchlorate toxicity, studies that have defined no-effect levels for most effects associated with toxicity, and studies that have refined our knowledge of perchlorate effects within the body.

In addition to the wealth of animal knowledge, we have a considerable

amount of human data that support the view that current environmental levels of perchlorate are well below those levels that have been associated with effects on thyroid hormones and/or thyroid function. Both occupational and clinical studies have been conducted to determine if and how various levels affect human health, what dose or airborne concentrations are required to elicit measurable effects, and, importantly, what no-effect levels are. In summary, we have a sound database for perchlorate, which increases the confidence and support for the RfD that is established.

The Scientific Process at Work—Why the Public Benefits

What we have witnessed over the course of the past decade regarding perchlorate should be reassuring to both scientific researchers and the general public. Minute amounts of previously undetectable perchlorate in some water sources should not be portrayed as a public health crisis. Progress in technological capability has led us to learn about the exact quantity of perchlorate in water. Similarly, it has been an advancement in toxicological science and a commitment to the scientific process that has led us to learn a significant amount about how perchlorate works, at what levels it exerts effects, and critically, at what levels it does not exert effects. It is because of the advancement in our scientific knowledge that RfD, one that is associated with a minimal amount of uncertainty, will be established.

The scientific process has proceeded over the last 10 years for perchlorate through a unique and collaborative effort between public and private sectors. What has been perhaps most surprising is the speed with which we have gleaned this incredible amount of scientific information. It is highly unusual to have complex and time-consuming laboratory experiments planned, implemented, completed, and published within the time frame that has occurred for perchlorate. It is difficult to understand how a process as transparent and objective could be criticized on any level, and it is anticipated that what emanates as a final RfD will be scientifically supported as well as any other regulated chemical in commerce today. While science can be slow and frustrating at times, if allowed to develop as it has for perchlorate, ultimately the benefits to society, in the form of scientifically sound safe exposure levels, are well worth the effort.

A considerable amount of data has been garnered about perchlorate, data that encompass both animal testing and human studies.

Collectively the data continue to show that the thyroid is by far the most sensitive target organ for perchlorate, and other toxicities that do not stem from perchlorate's action on the thyroid are not evident. The collective studies also demonstrate that effects are seen primarily at high doses of perchlorate relative to environmental exposures and that concentrations in drinking water should not pose a risk to humans. While it is not known what the final RfD for perchlorate will be, the scientific data and knowledge that has been generated will enable the EPA to establish a safe exposure level that will identify the most sensitive individual and protective endpoint known, yet also use the knowledge that has been generated to reduce any remaining uncertainty in the value to a minimum.

Glossary

Anion—An atom or radical with a negative charge.

Dose-response—The relationship between the amount of an agent applied or administered and the corresponding response of the target organ or tissue.

EWG—Environmental Working Group, a Washington D.C.-based activist environmental organization.

Histopathology—A branch of science that addresses the functional and structural manifestations of disease, particularly at the tissue level through microscopic analysis.

Hyperplasia—Excessive proliferation of normal cells or increase in cell number.

Hyperthyroidism—Excessive activity of the thyroid gland.

Hypertrophy—Enlargement of an organ, tissue, or cells as a result of an increase in cell size.

Hypothalamic-pituitary axis—The functional and biochemical interrelation between the hypothalamus, and pituitary and other endocrine glands, most often construed to include the thyroid and adrenal glands.

Hypothyroidism—Deficiency of thyroid activity.

Interspecies variability—The range of variation in response within a particular species.

Iodine—A nonmetallic element essential in human physiology and nutrition.

Mechanistic—In referring to mechanism of action, the means by which a biologically active material (e.g., chemicals, drugs) interacts with the cell or cellular components to elicit a response.

mg/kg/bw/day—This term is used in toxicology, including safety evaluations, and occasionally in pharmacology to describe the amount of chemical to which someone is exposed; weight of chemical per kilogram of body weight.

Neonate—A newborn; generally including the first four weeks of life.

Oxidizing agent—A chemical that is capable of donating electrons; when it occurs with another chemical, it is known as an oxidation-reduction (redox) reaction.

PBPK—Physiologically-based pharmacokinetics – Pharmacokinetics is the study of the time course of the absorption, distribution, metabolism, and excretion of drugs or chemicals in the body through the measurement of concentrations of metabolites in organs, tissues, or other biological matrices. PBPK differs from classical models in that real tissue, organs and body regions are used and as such are more realistic.

Perchlorate—The subject of this report, perchlorate is a contaminant in ground and surface waters whose occurrence results from the dissolution of ammonium, potassium, magnesium, or sodium perchlorate salts.

PPB—Parts per billion—quantitative expression often used to describe the concentration of a substance in air, water, or soil. Equivalent to micrograms per liter (μg/L) or micrograms per kilogram (mg/kg).

PPM—Parts per million. Equivalent to milligrams per liter (mg/L) or milligrams per kilogram (mg/kg).

PSG—Perchlorate Study Group, an interindustry group of company representatives who focus is the development of toxicological studies for enhanced understanding of perchlorate's toxicity and mechanism of action.

Pup—In this document, pup refers to a newborn rat.

RfD—Reference Dose – An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The RfD is generally used in EPA's noncancer health assessments.

Toxicodynamics—The relationship between toxicant dose and effect or response, with specific emphasis on the mechanism of action. Toxicodynamics deals with the study of physiological, biochemical, and molecular effects of toxicants.

Toxicokinetics—The study of the absorption, distribution, and elimination of toxic compounds in the living organism, with emphasis on the route by which these processes occur.

TSH—Thyroid-stimulating hormone which is produced in the pituitary gland.

T3—Triiodothyronine, one of the thyroid hormones

T4—Thyroxine, one of the thyroid hormones

Uncertainty factor (UF)—One of several, generally 10-fold factors, used in operationally deriving the RfD and RfC from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, i.e., interhuman or intraspecies variability; (2) the uncertainty in extrapolating animal data to humans, i.e., interspecies variability; (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure, i.e., extrapolating from subchronic to chronic exposure; (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the data base is incomplete.